REMARKS

Reconsideration of the rejection of or objection to all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claims 1, 2, 9, 10 and 13-16 have been amended above to further specify that the in vivo hydorlysable ester of these claims is formed on an available carboxy group of the compound of Formula Ia or Ib as defined in these claims. Support for this amendment is found in the specification at page 24, line 20 to page 25, line 9, and in particular at page 25, lines 8-9. Entry of these amendments is therefore respectfully requested.

The foregoing claim amendments are made without abandonment or prejudice to Applicant's right to prosecute any subject matter thereby deleted in one or more continuing applications. Following entry of these amendments, claims 1-3, 5-10 and 13-16 remain pending in this application.

Prosecution Background

Briefly, to place the outstanding Action and the present Amendment and Response in context of the prosecution of this application, a written restriction requirement was made on September 9, 2002. Applicant filed a response to the restriction requirement on January 6, 2003, including a preliminary amendment that was believed to limit elected claims 1-3, 5-10 and 12 to an appropriate scope of invention. In the next Action mailed May 14, 2003, claims 1-3, 5-10 and 12 were objected to for containing non-elected subject matter, but the Examiner noted that claims drawn solely to the elected invention "would appear allowable."

A telephone interview was held on November 13, 2003 between the Examiner and the undersigned during which the undersigned explained that the preliminary amendment of January 6, 2003 already limited the claims to the elected subject matter. It is understood that the Examiner agreed and allowability of the elected subject matter was indicated. A summary of that telephone interview was set forth in Applicant's Response filed November 14, 2003.

The next Action mailed February 27, 2004 stated that the previous amendments had overcome the objections to elected claims 1-3 and 5-10, but newly rejected the method of claim 12 as not being enabled by the specification. Applicant's Amendment and Response of May 27, 2004 cancelled claim 12 and replaced it with new method claims 13-16.

In the present Action mailed August 24, 2004, new method claims 13-16 have been entered and are only objected to for depending on a rejected base claim. However, claims 1-3 and 5-10 have now been newly rejected under 35 U.S.C. § 112, the Examiner noting that "the specification, while being enabling for amide derivatives of Formula Ia or Ib, does not reasonably provide enablement for all esters of these compounds." In particular, this rejection appears to focus on both the claim term "amide derivative" and the claim term "or in vivo cleavable ester thereof."

Thus, in making this rejection the Examiner makes the following assertions, among others, to which numbering has been assigned by the undersigned for convenience of reference in the discussion that follows:

1. Under the heading "The State of the Prior Art" the Examiner asserts that "the state of the prior art is that there are numerous ester derivatives of amide compounds" and that "these derivatives include aliphatic, aromatic, carbocyclic, heterocyclic ect" (Action at page 3);
2. Under the heading "The predictability or lack thereof in the art" the Examiner asserts that "there would be little predictability in the art of which modifications may be made to a amide compound, which would retain its capability as a pharmaceutical grade compound," and that *in vitro* and *in vivo* testing would be involved "to determine which compounds exhibit the desired pharmacological activities" (Action at page 3);
3. Under the heading "The amount of direction or guidance present" the Examiner asserts that "the term 'ester' may encompass a great number of compounds related to amide compounds, however, without some guidance as to what changes may be made to the amide compounds, there would be little predictability in making and/or using such 'amides'" (Action at page 3);
4. Under the heading "the breadth of the claims" the Examiner asserts that "the breadth of the claims is that the ester derivative could include unlimited number of compounds that are heterocyclic, non-heterocyclic, aliphatic etc." (Action at page 4);
5. Under the heading "The quantity of experimentation needed" the Examiner asserts that "the quantity of experimentation needed is undue experimentation" and that "one

of skill in the art would need to determine what listed derivatives would be prepared by the method described and would furthermore then have to determine whether the claimed process would produce amide compound" (Action at page 4); and

6. Under the heading "The level of skill in the art" the Examiner asserts that the level of skill in the art is high, but due to the unpredictability in the pharmaceutical art, "each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which derivatives exhibit the desired pharmacological activity" (Action at page 4).

From this, the Examiner concludes:

> Thus, the specification fails to provide sufficient support of the broad use of the term "derivative" because no formula is provided. As a result necessitating one of skill to perform an exhaustive search for which derivatives can be prepared can be in order to practice the claimed invention.

(Action at page 4, middle paragraph). This ground for rejection is respectfully traversed.

The "amide derivative" is Defined by Formula Ia or Ib

It is asserted in the Examiner's conclusion above that the broad use of the term "derivative" is not sufficiently supported by the specification "because no formula is provided," and that the skilled person must "perform an exhaustive search for which derivatives can be prepared" to practice the invention. To the contrary, it is believed clear that the "amide derivative" of the claims is defined by Formula Ia or Formula Ib.

Thus, the only use of the term "derivative" in the pending claims with respect to the claimed compounds is in context of "an amide derivative of the Formula Ia . . .", "an amide derivative of the Formula Ib . . ." and "an amide derivative of the Formula Ia or Ib." The "amide derivative" is the compound of the Formula Ia or the compound of the Formula Ib, the metes and bounds of which are definitively set forth by the definitions of the variables within these claims. Thus, it is respectfully submitted, that the term "derivative" as used in the claims does not lack specification enablement. In fact, the Examiner acknowledge as much in the introduction of the non-enablement rejection at page 2, where it is stated that

"the specification, while being enabling for amide derivatives of Formula Ia or Ib . . ." (emphasis added).

The Term "in vivo cleavable ester thereof" Does Not Render the Claim Non-Enabled

In view of the above discussion, it will be presumed that the non-enablement rejection was intended to be based on the reference to the term "ester thereof." Again, the rejection begins with the statement at page 2 of the Action, that "the specification, while being enabling for amide derivatives of Formula Ia or Ib, does not reasonably provide enablement for all esters of these compounds" (emphasis added). In point numbered 1 above, it is noted that "the state of the prior art is that there are numerous ester derivatives of amide compounds." In point numbered 3 above, it is noted that the "term 'ester' may encompass a great number of compounds related to amide compounds" (emphasis added). In point numbered 4 above, it is noted that "the breadth of the claims is that the ester derivative could include unlimited number of compounds that are heterocyclic, non-heterocyclic, aliphatic etc." (emphasis added).

However, the claims do not encompass any and all esters of the amide compounds, as the Examiner seems to be implying, but rather are limited to a "pharmaceutically acceptable . . . in vivo cleavable ester thereof." As will be demonstrated below, the term "pharmaceutically acceptable . . . in vivo-cleavable ester thereof" is clearly enabled by guidance provided by the specification disclosure and the general knowledge in the art with respect in vivo-cleavable esters and the broader prodrug art of which they are a part. Nevertheless, in order to expedite the prosecution of this application to allowance, this recitation has been made even more specific by the above amendments, by which this phrase has been modified so the that the claims now read, in part, "An amide derivative of the Formula Ia [or Ib or both; Formula and definitions omitted] . . . or a pharmaceutically acceptable . . . in vivo-cleavable ester formed on an available carboxy group thereof."

The basis for the non-enablement rejection based on the term "in vivo-cleavable ester" is not understood, when one considers the specification disclosure and the extensive use of the terms, concept and structure of in vivo cleavable (or hydrolysable) esters and "pro-drugs" throughout the pharmaceutical literature and patents (including patent claims).

First of all there is direct specification support and enablement for "in vivo-cleavable esters" as a type of pro-drug at page 24, line 20 to page 25, line 9, which (for the Examiner's convenience) reads as follows:

> Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:
>
> a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
>
> b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
>
> c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
>
> d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
>
> e) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984).
>
> **Examples of such pro-drugs may be used to form in-vivo-cleavable esters of a compound of the Formula Ia or Ib. An in-vivo-cleavable ester of a compound of the Formula Ia or Ib containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include** (1-6C)alkoxymethyl esters, for example methoxymethyl; (1-6C)alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

(Emphasis added).

The specification thus cites five literature references that were available to the art at the time the present invention was made, which detail the concept and design of prodrugs, including prodrugs in ester form. Moreover, a recent search of the U.S. PTO patent database for patents granted in the years 1975 to date identified 1704 U.S. patents in which one or more claims include the term "prodrug," of which 518 issued before the March 16, 1999 priority date claimed for this application. A further search for patents granted in the years 1975 to date identified 51 U.S. patents in which one or more of the claims includes one of the

terms "in vivo" or "in-vivo" in combination with one of the terms "hydrolyzable," "hyrolysable" or "cleavable" and the term "ester," 42 of which issued before the March 16, 1999.

It is respectfully submitted that this multitude of patents with claims including "prodrugs" or the term "in vivo cleavable ester" or the equivalent, makes clear that the meaning and structure of "in vivo-cleavable ester" and of prodrugs in general is and was well understood by persons skilled in the pharmaceutical arts. Most of these patents include significantly less guidance than the present specification but, on the other hand, make clear that persons skilled in the art will have no difficulty in understanding and practicing the preparation and use of prodrugs, including in vivo hydrolyzable or cleavable esters. Some of these references, like the present specification, refer the reader to literature references for more details if needed. Excerpts from a few of the many patents including specific reference to hydrolysable or cleavable esters as prodrugs, are as follows:

U.S. Patent 6,465,467 (issued October 15, 2002)

> The term "prodrug forms" means a pharmacologically acceptable derivative, at such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15. (Col. 8, lines 21-26).

U.S. Patent 5,866,568 (Issued February 2, 1999)

> It will further be appreciated that a compound of the formula I may be chemically modified such that in vivo it is converted into a parent compound of the formula I (for example, by hydrolytic, oxidative or enzymatic cleavage). Such chemically modified compounds are commonly referred to as prodrugs and may be, for example, metabolically labile ester or amide derivatives of a parent compound having a carboxylic acid group (or a metabolically labile ester of a parent compound having an hydroxy group). It is to be understood that the present invention also concerns any such prodrugs, including metabolically labile ester or amide derivatives of compounds of the formula I. (Col. 3, line 63 to col. 4, line 6).

* * * * *

Examples of metabolically labile ester derivatives of a carboxy group are esters formed with alcohols such as (1-6C)alkanols, for example methanol, ethanol, propanol and isopropanol; indanol; adamantol; (1-6C)alkanoyloxy(1-4C)alkanols such as pivaloyloxymethyl; glycolamides; (S-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol; and (1-4C)alkyloxycarbonyl(1-4)alkanols.

Examples of metabolically labile amide derivatives of a carboxy group include amides formed from ammonia and amines such as (1-4C)alkylamine, for example methylamine, di(1-4C)alkyl amines, (1-4C)alkoxy(1-4C)alkylamines such as methoxyethyl amine, phenyl(1-2C)alkylamines such as benzylamine; and amino acids such as glycine or an ester thereof.

It will be appreciated that where sub-groups of compounds of the invention, or particular or preferred groups of compounds of the invention or specific compounds of the invention are referred to, these groups include prodrugs of said compounds, such as metabolically labile esters or amides. (Col. 11, lines 22-41).

* * * * *

Additionally, a compound of the formula I may be converted into a prodrug (for example, a metabolically labile ester or amide) by methods well known in the art. For example, a pharmaceutically acceptable metabolically labile ester or amide may be formed respectively by estcrifying a compound of the formula I bearing a carboxylic acid (or hydroxy) group or reacting the carboxylic acid group (or a reactive derivative thereof) with the appropriate amine, using conventional techniques. (Col. 14, lines 35-43).

U.S. Patent 5,726,182 (issued March 10, 1998)

The term "prodrug", as of the compounds of formula I, refers to derivative compounds that are rapidly transformed in vivo to yield the parent compound of the formula I, as for example by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E. B. Roche, Pergamon Press: New York (1987). It is intended that these references, and any others cited throughout this specification, are incorporated herein by reference.

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of

prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found in the book "Pro-drugs as Novel Delivery Systems", by Higuchi and Stella, cited above. (Col. 21, lines 10-31).

U.S. Patent 5,616,591 (issued April 1, 1997)

It should be understood that the present invention includes prodrug forms, such as ester, acetal and/or mixed acetal derivatives of the compounds of formula I. For example, such derivatives have been documented in Design of Prodrugs, edited by H. Bundgard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder et al. (Academic Press, 1985). Further, it is understood that any moiety at R_6 and/or R_7 that will be cleaved in vivo to provide an acidic R_6 and/or R_7 moiety is within the spirit and scope of this invention. (Col. 3, lines 57-67)

U.S. Patent 5,468,757 (issued November 21, 1995)

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically clearable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. (Col. 7, line 62 through col. 8, line 14)

Thus, in addition to the disclosure in the present specification at pages 24-25, the pharmaceutical art is replete with guidance (both in literature and issued patents) on making prodrugs of pharmaceutical compounds, including in ester form which would be "*in vivo* cleavable."

The specific assertions made by the Examiner (as numbered above) can each be answered and overcome by consideration of the present specification disclosure, and what was clearly known in the art as evidenced by the above patents and literature references:

In point 1, the Examiner asserts that the state of the prior art is that there are "numerous ester derivatives of amide compounds," and that "these derivatives include aliphatic, aromatic, carbocyclic, heterocyclic" etc. groups. While there may be numerous, diverse "ester derivatives" of "amide compounds" in general, the present claims are more specifically directed toward "amide derivatives" as particularly defined by Formula Ia or Ib, and "pharmaceutically acceptable . . . in vivo-cleavable esters formed on an available carboxy group thereof," with respect to which there is guidance provided in the specification and more than ample information in the art prior at the time the priority date of this application. The literature and patent evidence discussed above makes clear that persons skilled in the art would have no problem understanding the meaning of this claim term and putting it into practice.

In point 2, the Examiner asserts that "there would be little predictability in the art of which modifications may be made to a amide compound, which would retain its capability as a pharmaceutical grade compound," and that *in vitro* and *in vivo* testing would be involved "to determine which compounds exhibit the desired pharmacological activities." However, the specification already provides guidance with respect to specific ester forming compounds by which the claimed invention can be practiced, and many other suitable ester forming compounds could be found in the literature cited in the specification and the numerous other literature and patent references already existing in the art at the time of this invention. If the skilled person chooses to venture further with other ester forming compounds, then the level of skill in the art was certainly such that the skilled person was capable of carrying out whatever *in vitro* and/or *in vivo* tests were felt necessary to test for the desired pharmacological activities. Such tests were routine, and even if lengthy or tedious to carry out, this does not constitute "undue experimentation" (see further below).

In point 3, the Examiner asserts that "the term 'ester' may encompass a great number of compounds related to amide compounds," but that "without some guidance as to what changes may be made to the amide compounds, there would be little predictability in making

and/or using such 'amides.'" Attention is first called to the discussion of point 1 above, making clear that the claims are not directed to just any "ester" of any amide compound. Rather, the claims are far more specifically directed toward "amide derivatives" as particularly defined by Formula Ia or Ib, and "pharmaceutically acceptable . . . in vivo-cleavable esters formed on an available carboxy group thereof," with respect to which there is guidance provided in the specification and more than ample guidance available in the art at the time the priority date of this application.

In point 4, the Examiner asserts that "the breadth of the claims is that the ester derivative could include unlimited number of compounds that are heterocyclic, non-heterocyclic, aliphatic etc." Again, attention is drawn to the discussion of points 1 and 3 above, that the claims are not directed to just any "ester derivative," but rather to toward "amide derivatives" as particularly defined by Formula Ia or Ib, and "pharmaceutically acceptable . . . in vivo-cleavable esters formed on an available carboxy group thereof."

In point 5 the Examiner asserts that "the quantity of experimentation needed is undue experimentation" and that "one skilled in the art would need to determine what listed derivatives would be prepared by the method described and would furthermore then have to determine whether the claimed process would produce amide compound" This point is not clearly understood. As noted above, the "amide derivatives" recited in the claims are particularly defined by Formula Ia or Ib. Guidance for the preparation of these amide derivatives is provided in the specification, and the chemistry involved to make the claimed compounds is well within the skill of the art, particularly when considered together with the specification guidance. If the Examiner is intending to address the making of in-vivo-cleavable ester of the claimed compounds, the specification at pages 24-25 recites a number of reactants that can be used to form the "in vivo cleavable esters formed on any available carboxy group" of the amid derivative as claimed, and many other reactants for forming such prodrug esters are exemplified in the cited literature. Clearly, a skilled pharmaceutical chemist would know how to make an ester from these reactants, or would know how to find suitable reaction schemes in the available literature.

In point 6 the Examiner asserts that the level of skill in the art is high, but due the unpredictability in the pharmaceutical art, "each embodiment of the invention is required to

be individually assessed for physiological activity by in vitro and in vivo screening to determine which derivatives exhibit the desired pharmacological activity" It is presumed that the Examiner is again (as in points 2 and 5 above) asserting that "undue experimentation" would be required to make the determinations noted. Again, it should be clear from the above discussion that the relevant concepts and structures were so well known and reported in the patent and published literature that persons skilled in the art would have had no problem understanding and practicing the invention as claimed. The Federal Circuit has repeatedly made clear that the emphasis is on "undue", not whether some experimentation may be required. See, for example, *PPG Industries Inc. v. Guardian Industries Corp.* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

> Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
>
> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Considering the extensive knowledge in the art at the time of the present invention pertaining to prodrugs in general and *in-vivo* cleavable or hydrolysable esters, in particular, and the guidance provided by the present specification, any experimentation that might have been required to practice this embodiment of the present invention would have been, at worst, a routine matter.

Therefore, it is submitted that the term "in-vivo cleavable ester formed on any available carboxy group," in context of this invention, would have been clearly understood by persons skilled in this art, and such persons would have been able to practice this embodiment of the invention without undue experimentation at the time the application for this invention was filed. Accordingly, it is respectfully requested that these section 112 grounds for rejection be withdrawn.

Conclusion

The sole ground for rejection remaining in this application, first raised in the presently outstanding Action, is that claims 1-3 and 5-10 are not enabled by the specification, with respect to the term derivative and "in vivo-cleavable ester." It has been shown above that insofar as this rejection is based on the term "derivative," this appears to be in error, since the only reference to derivative with respect to the claimed compounds is in the term "amide derivative" which the Examiner at page 2 has specifically acknowledged is enabled. Insofar as the non-enablement rejection is based on the term "in vitro-cleavable ester," it has been demonstrated above that the specification and literature references cited therein provide ample guidance with respect to suitable ester forming compounds to fully enable the claims, and the published and patented literature is replete with further guidance and examples that provide still further enablement. The fact that some experimentation may be necessary if one chooses to venture beyond the guidance and ester forming compounds disclosed in the specification and the art at the time the priority application was filed, the case law is clear that the emphasis should be on whether the experimentation is "undue." As also shown above, the chemistry involved and the *in vitro* and *in vivo* tests involved are routine, and clearly do not rise to the level of "undue" experimentation.

Applicant is anxious to expedite the prosecution of this application to allowance. Therefore, in the event that the Examiner still believes, after consideration of the above, that any ground for rejection remain outstanding, it is respectfully and urgently requested that the Examiner telephone the undersigned for a telephonic or personal interview so that any such remaining issues can be resolved immediately to place this application in condition for allowance.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: January 24, 2005 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk